Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

tolvaptan 15mg, 30mg, 45mg, 60mg and 90mg tablets (Jinarc®)

Otsuka Pharmaceuticals (UK) Ltd SMC No. (1114/15)

04 December 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission under the orphan process

tolvaptan (Jinarc®) is accepted for use within NHS Scotland.

Indication under review: to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease.

In a phase III placebo-controlled study tolvaptan, after 3 years, had significantly slowed the rate of disease progression as measured by impact on the rate of increase in total kidney volume (TKV) in ADPKD patients who were deemed to be at high risk of disease progression and had relatively preserved renal function. The study inclusion criteria included (list not exhaustive): age 18 to 50 years old, TKV ≥750ml and creatinine clearance ≥60ml/minute.

This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of tolvaptan. This advice is contingent upon the continuing availability of the patient access scheme or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

To slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease in adults with chronic kidney disease (CKD) stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease.

Dosing Information

The initial daily dose is 60mg tolvaptan as a split-dose regimen (45mg taken upon waking and before breakfast and 15mg taken eight hours later). The initial dose is to be titrated upward to a split-dose regimen of 90mg tolvaptan (60mg+30mg) daily and then to a target split-dose regimen of 120mg tolvaptan (90mg+30mg) daily, if tolerated, with at least weekly intervals between titrations. Dose titration has to be performed cautiously to ensure that high doses are not poorly tolerated through overly rapid up-titration. Patients may down-titrate to lower doses based on tolerability. Patients have to be maintained on the highest tolerable tolvaptan dose.

The morning dose should be taken at least 30 minutes before the morning meal. The second daily dose can be taken with or without food.

The safety and efficacy of tolvaptan in CKD stage 5 have not been adequately explored and therefore tolvaptan treatment should be discontinued if renal insufficiency progresses to CKD stage 5.

Therapy must be interrupted if the ability to drink or the accessibility to water is limited. Tolvaptan must not be taken with grapefruit juice. Patients must be instructed to drink sufficient amounts of water or other aqueous fluids.

Tolvaptan treatment must be initiated and monitored under the supervision of physicians with expertise in managing ADPKD and a full understanding of the risks of tolvaptan therapy including hepatotoxicity and monitoring requirements.

Product availability date

01 June 2015
Tolvaptan meets SMC orphan equivalent criteria.

Summary of evidence on comparative efficacy

Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary disease, characterised by the formation of fluid-filled renal cysts, which may progress to end-stage renal disease (ESRD). The physiological neuropeptide arginine vasopressin has been linked to the formation and growth of kidney cysts in ADPKD through stimulation of adenosine 3′,5′-cyclic monophosphate (cAMP) production. Tolvaptan is a non-peptide specific antagonist of arginine vasopressin at the V2 receptors in the distal portions of the nephron.[1] It is the first disease modifying treatment for ADPKD.

The evidence supporting the marketing authorisation is from the pivotal study and its open-label extension study.

TEMPO 3:4 was a phase III, multicentre, double-blind, randomised, placebo-controlled study in adults with ADPKD.[2] Eligible patients were 18 to 50 years old with a diagnosis of ADPKD according to the Ravine criteria i.e. patients with a family history of ADPKD (i.e. at 50% risk for the disease) had to have ≥3 cysts in each kidney if detected by ultrasound or ≥5 cysts in each kidney if by computed tomography or magnetic resonance imaging (CT/MRI); patients with no family history of ADPKD had to have bilateral renal enlargement, ≥10 cysts in each kidney plus the absence of other manifestations suggesting a different renal cystic disease. In addition all patients were required to have a total kidney volume (TKV) ≥750mL (measured using MRI) and a creatinine clearance ≥60mL/minute.[2]

A total of 1,445 patients were randomised centrally in a 2:1 ratio to receive three years treatment with tolvaptan (n=961) or placebo (n=484), with stratification according to presence or absence of hypertension, creatinine clearance (<80 versus ≥80mL/minute), TKV (<1,000mL versus ≥1,000mL), and geographic area. The initial daily dose of tolvaptan was 60mg (45mg in the morning and 15mg in the afternoon) and this was increased, if tolerated, after one week to 90mg (60mg in the morning and 30mg in the afternoon) and after another week to 120mg (90mg in the morning and 30mg in the afternoon).[2]

The primary outcome was the annualised rate of change in TKV, (for both kidneys normalised as a percentage) from baseline for tolvaptan (combining all doses) relative to placebo at three years.[2] The primary analysis included only patients who were evaluated for the primary efficacy endpoint, key secondary composite endpoint, and polycystic kidney disease outcomes at the last scheduled visit (Month 36) during the treatment period.[1] The primary analysis population therefore comprised 90% (1,307/1,445) of the intention to treat (ITT) population; 88% (842/961) of tolvaptan patients and 96% (465/484) of placebo patients. A total of 138 patients were excluded due to early withdrawal and/or a lack of measurable follow-up MRI scans.[2]

After three years the rate of increase in TKV was significantly lower in the tolvaptan group: 2.8% per year (95% confidence interval [CI]: 2.5 to 3.1) than in the placebo group: 5.5% per year (95% CI: 5.1 to 6.0), giving a ratio of the geometric mean of 0.97 (95% CI: 0.97 to 0.98; $p<0.001$).[1,2] A mixed-model, repeated-measures, sensitivity analysis confirmed the primary analysis: the least-squares mean change in TKV over the 3-year period was 9.6% with tolvaptan versus 19% with placebo; $p<0.001$. This represented a relative reduction of 49% in the rate of increase of TKV with tolvaptan versus placebo. The effect was greater during the first year than during the second and third years. Subgroup analyses according to the following baseline characteristics were pre-specified: sex, age (<35 years versus ≥35 years), TKV (<1,500mL versus ≥1,500mL), estimated creatinine clearance (<80mL/min versus ≥80mL/min) and hypertension status (absent versus present). Tolvaptan reduced the rate of increase of TKV compared with placebo in all subgroups.[2]

The key secondary outcome was a composite of four endpoints. It was designed to reflect time to investigator-assessed clinical progression and was defined as: worsening kidney function (a 25% reduction in the reciprocal of the serum creatinine level from the value at the end of the dose-adjustment period, reproduced after at least two weeks); clinically significant kidney pain necessitating medical leave, pharmacologic treatment (opioid or last-resort analgesic agents), or invasive intervention; worsening hypertension (changes in blood-pressure category, as defined in the protocol, or worsening hypertension requiring an increase in hypertensive treatment); and worsening albuminuria (according to pre-defined sex-specified categories). In the tolvaptan group there were significantly fewer clinical progression-related events per 100 person-years of follow-up than in the placebo group (44 versus 50 events; hazard ratio [HR], 0.87; 95% CI, 0.78

to 0.97; p=0.01). Analysis of time to first event gave a HR of 0.83 (95% CI, 0.72 to 0.94; p=0.005).[2] Treatment effects varied greatly across the components. Compared with placebo, tolvaptan reduced worsening renal function and severe renal pain components, but there was no benefit in the worsening hypertension or worsening albuminuria components.[1,2]

Table 1: Results of component endpoints in key secondary composite outcome[1]

	Worsening renal function (reciprocal of serum creatinine)		Worsening clinically significant renal pain necessitating medical leave, pharmacological treatment or invasive intervention		Worsening hypertension (requiring further treatment)		Worsening albuminuria	
	Tolvaptan	Placebo	Tolvaptan	Placebo	Tolvaptan	Placebo	Tolvaptan	Placebo
No of patients	917	476	961	483	961	483	961	483
Events per 100 follow-up years	2	5	5	7	31	32	8	8
HR for tolvaptan versus placebo (95% CI) p value)	0.39 (0.26 to 0.57) <0.0001		0.64 (0.47 to 0.89) 0.007		0.94 (0.81 to 1.09) 0.422		1.04 (0.84 to 1.28) 0.742	

No=number; HR=hazard ratio; CI=confidence interval

Change in renal function (measured by the reciprocal of the serum creatinine level from the end of dose escalation to month 36) was also measured as a non-composite secondary outcome. Treatment with tolvaptan statistically significantly slowed renal function decline by approximately one third compared with placebo, with a reduction in the rate of deterioration of 1.20mg/mL^{-1} per year (95% CI, 0.62 to 1.78; p<0.001). Analysis of the annual estimated GFR (eGFR) slope, using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, gave similar results: a reduction in the rate of deterioration of 0.98mL/min/1.73m^2 per year; (95% CI: 0.60 to 1.36; p<0.001).[2]

No other planned secondary outcomes showed significant benefit for tolvaptan over placebo including effects on change from baseline on control of blood pressure regardless of whether the patient was normotensive or hypertensive at baseline, or on the renal pain scale.[1] The mean baseline pain score was very low, <1 (scale of 0 to 10 with zero representing no pain).[2] Quality of life was not assessed.

An ongoing, open-label extension study, TEMPO 4:4, includes patients who had completed TEMPO 3:4. Interim analysis conducted after two years indicated that the effect of tolvaptan on eGFR was maintained.[1]

Summary of evidence on comparative safety

In the TEMPO 3:4 study almost all patients in both the tolvaptan and placebo groups reported at least one adverse event: 98% and 97%, respectively. Patients in the tolvaptan group had significantly higher rates of adverse events related to increased aquaresis than those in the placebo group: thirst (55% versus 20%), polyuria (38% versus 17%), nocturia (29% versus 13%), daytime urinary frequency (23% versus 5.4%) and polydipsia (10% versus 3.5%).[2]

Serious adverse events were reported in 18% of patients receiving tolvaptan and in 20% of patients receiving placebo.[1] Serious adverse events that were more common in patients receiving tolvaptan than placebo were increased alanine aminotransferase (0.9% versus 0.4%); increased aspartate aminotransferase (0.9% versus 0.4%); chest pain (0.8% versus 0.4%) and headache (0.5% versus 0). [2]

A higher proportion of patients receiving tolvaptan than placebo discontinued the study because of adverse events: 15% (148/961) versus 5.0% (24/484), respectively. In patients receiving tolvaptan the proportion of patients that discontinued study drug due to aquaresis-related symptoms was 8.3% (80/961) and due to liver function abnormalities was 1.2% (12/961).[2] A reversible reduction in GFR has been observed in ADPKD studies at the initiation of tolvaptan treatment.[1]

The overall incidence of serious hepatic adverse events was higher in patients receiving tolvaptan than placebo: 2.3% (22/961) versus 1.0% (5/483). Two patients receiving tolvaptan during TEMPO 3:4 and one patient receiving tolvaptan in the extension study, TEMPO 4:4, were deemed to have potentially serious liver injury. The onset of hepatocellular injury (transaminase values exceeding 3×upper limit of normal), was characteristically observed after at least three months of treatment, but could occur after one year. The European Medicines Agency (EMA) has stated that tolvaptan has the potential to cause liver injury that could progress to liver failure and that the number of patients with ADPKD currently exposed is insufficient to rule out less common but severe hepatic toxicity. The EMA has estimated that the incidence of acute liver failure in ADPKD patients chronically treated with tolvaptan could be approximately 1 in 4,000.[1] The Summary of Product Characteristics for tolvaptan includes monitoring and discontinuation recommendations for hepatic injury.[3]

Summary of clinical effectiveness issues

ADPKD is a progressive disease that may lead to ESRD, hypertension, pain, kidney stones, haematuria and infections. Normal renal function is often maintained for many years due to compensatory hyperfiltration by intact nephrons and only declines when most nephrons have been destroyed. Extra-renal complications of ADPKD include cardiac and vascular abnormalities and hepatic fibrosis.[4,5] Disease severity varies substantially among patients: some experience renal failure soon after diagnosis whilst others have a mild disease course throughout life. Clinical features usually begin in the third to fourth decade, but cysts may be detectable much earlier as an incidental finding or during screening of affected families. Up to 50% of patients with ADPKD require renal replacement therapy (dialysis or transplant) by the age of 60 years.[1,3] Tolvaptan is the first treatment licensed to slow the progression of ADPKD.

Tolvaptan meets SMC orphan equivalent criteria. Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely the lack of an effective treatment.

In the pivotal study in patients with a relatively large kidney volume, but reasonably well preserved renal function, the primary outcome of change in TKV was approximately halved after three years treatment with tolvaptan compared with placebo: 9.6% versus 19%, respectively, with a larger effect during the first year than during the second and third years.[2] Increase in TKV correlates to growth in cyst volume and was considered to be an appropriate surrogate for disease progression by the EMA.[1,4] The key secondary composite outcome, reflecting time to disease progression, found significantly fewer disease-related events per 100 person-years of follow-up with tolvaptan than placebo.[2] The rate of reduction in eGFR was significantly reduced by about one third with tolvaptan compared with placebo, although the absolute difference was small at approximately 1mL/min/1.73m^2 per year. Over time, if the treatment effect continues, there is the potential for ESRD to be delayed. Although tolvaptan statistically significantly improved renal pain that required medical leave/drug treatment/invasive intervention by two events per 100 person-years of follow-up compared with placebo (a component of the composite key secondary outcome), there was no benefit over placebo for the non-composite secondary outcome which measured all renal pain. There was also no improvement over placebo in hypertension or albuminuria although the company has indicated that these results are difficult to interpret due to high proportions of patients with these conditions at baseline and high usage of antihypertensive medicines.[1,2]

Limitations of the evidence include a substantial level of missing data. The primary analysis included 88% of tolvaptan patients compared with 96% of placebo patients. The higher withdrawal rate in the tolvaptan group is a potential source of bias in favour of tolvaptan, since non-responders are more likely to have stopped treatment early and their results would not have been included in the analysis. The submitting company has provided analyses assuming 100% loss of efficacy of tolvaptan for all patients who withdrew from the study and these indicated that the results of the primary, secondary composite and eGFR outcomes would still be statistically significant.

The study population comprised patients at early stages (CKD stages 1 to 3) of the disease and the three years' study duration was too short to determine if treatment with tolvaptan would delay dialysis or renal transplant. The lack of data in later stages of ADPKD and the missing study data make extrapolation of the study results problematic. Since eligible patients were aged 18 to 50 years, the effectiveness of tolvaptan in patients older than 50 years is not known.[2]

Quality of life in patients receiving tolvaptan has not been investigated. There was a higher incidence of adverse events related to water loss including thirst, polyuria, nocturia and daytime urinary frequency. Patients should be instructed to drink water or other aqueous fluids at the first sign of thirst in order to avoid excessive thirst or dehydration and also to drink one or two glasses of fluid before bedtime regardless of perceived thirst, and to replenish fluids overnight with each episode of nocturia.[3]

Clinical experts consulted by SMC considered that tolvaptan is a therapeutic advancement as it is the only licensed treatment for ADPKD, and that its place in therapy is in patients with large symptomatic cysts and deteriorating renal function. They considered that the introduction of tolvaptan may impact on the patient and on service delivery as increased monitoring would be required, including liver function tests, MRI scans and extra clinic visits. Blood testing for hepatic transaminases and bilirubin is required prior to initiation of tolvaptan, once a month for the first 18 months and then at regular 3-monthly intervals. Symptoms that may indicate liver injury

(such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, dark urine or jaundice) should be monitored. Fluid and electrolyte status must be monitored in all patients.[3]

SMC members noted the absence of a definition of 'rapidly progressing disease' in the Summary of Product Characteristics. While this may be clearly present in some patients, for example those with very high and rapidly increasing kidney volume, or with documented rates of decline in eGFR well in excess of the usual rates in ADPKD (mean rate of decline of CKD-EPI eGFR in the placebo group of TEMPO 3:4 was 3.7 ml/min/1.73m^2/year), the Committee agreed that national and/or international guidelines would be required to define the appropriate place in therapy for tolvaptan in AKPKD.

Summary of patient and clinician engagement

A Patient and Clinician Engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of tolvaptan, as an orphan equivalent medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Autosomal dominant polycystic kidney disease (ADPKD) is a life-threatening and incurable condition. The condition usually starts to adversely affect kidney function in relatively young people impacting on their working lives and their role in caring for children. Symptoms such as pain, recurrent urinary tract infections, extreme fatigue and cardiovascular events such as stroke and hypertension, all impact severely on quality of life.

- About 50% of patients will need dialysis or a kidney transplant. Dialysis is extremely limiting for patients in view of the associated time commitment and dietary restrictions impacting on them and the wider family.

- ADPKD can cause psychological distress around disease progression and subsequent consequences on the family. In particular, there is significant concern with respect to the autosomal dominant inheritance aspect of ADPKD where patients are aware of the possibility of passing the condition on to children.

- PACE participants emphasised that the availability of tolvaptan would give hope for patients as well as future generations of ADPKD sufferers.

- Clinicians were very supportive of tolvaptan but they expressed some uncertainty with respect to which group of patients would achieve most benefit. They highlighted that adopting tolvaptan would mean significant changes to practice, with more monitoring required and additional clinic visits. They also noted some uncertainty about the long term effects of tolvaptan.

- PACE participants considered there to be a high unmet need because there is no other treatment that currently addresses the underlying causes of ADPKD. Tolvaptan is disease specific and is the first treatment to potentially delay disease progression by slowing cyst growth and the decline in kidney function. Clinicians estimate that tolvaptan may defer the

onset of dialysis by an average of between 2 and 6 years, which would be extremely beneficial for patients.

Summary of comparative health economic evidence

The submitting company presented a cost utility analysis comparing tolvaptan to usual care/no active treatment in adult ADPKD patients with CKD stages 1 to 3 at initiation of treatment and evidence of rapidly progressing disease. The comparator was appropriate given SMC clinical expert responses.

A lifetime horizon was adopted in the analysis and used a patient- level simulation model. The model structure had two distinct parts: an ADPKD phase dependent on treatment where TKV and GFR were tracked up to the point when ESRD (or death) was reached, and an ESRD phase which was independent of treatment received (as treatment was no longer given). Patients could enter the ESRD phase in different states including conservative care, haemodialysis, peritoneal dialysis and transplant. The states in the ADPKD phase of the model reflected the CKD stages. The ADPKD phase also took separate account of clinically significant kidney pain, as measured in the TEMPO study. This was the only specific complication modelled; no other adverse events were captured in the base case.

In the ADPKD model, disease progression was tracked using TKV and eGFR and, importantly, eGFR was dependent on TKV with the relationship established using regression equations. The relative treatment effect of tolvaptan (31.6%) was applied in the model using renal function measured using the reciprocal of serum creatinine. The treatment effect was assumed to apply for the duration of treatment.

Utility values were estimated from literature sources. The values were 0.9 for stages 1 and 2, 0.87 for stage 3, 0.85 for stage 4, 0.688 for stage 5 pre-dialysis, 0.558 for ESRD on conservative care/hospital/community or home dialysis, 0.648 for ESRD on peritoneal dialysis.

Resource use included additional monitoring and testing costs associated with tolvaptan treatment, and also the background costs of disease management associated with the different phases of treatment and the costs of ESRD treatments, estimated using literature sources.

A Patient Access Scheme (PAS) was submitted by the company and has been assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount is offered on the price of the medicine. The base case cost per QALY with the PAS was £12,563 on the basis of a QALY gain of 0.92 and an incremental cost of £11,614. In terms of the clinical outcomes giving rise to the QALY gain, the company indicated that treatment with tolvaptan was associated with approximately 0.5 years less spent on dialysis, 20% fewer transplants and greater periods of time spent in stage 2, 3 and 4 and approximately 2 years less in the ESRD state. The key driver of the QALY gain was the mean delay in reaching ESRD of 3.7 years with tolvaptan.

There were a number of weaknesses and uncertainties associated with the analysis:

- As noted above, there are weaknesses with the clinical study. Further, while there is evidence of the treatment effect being maintained out to five years, there is uncertainty over this being sustained over the long term duration of the analysis, and sensitivity

analysis assuming less optimistic longer term outcomes had an impact on the ICER. Assuming rates that were 95%, 90% and 85% of the base case value increased the with-PAS ICERs to £16,565, £21,416 and £26,637 respectively. Further sensitivity to the longer term impact on treatment was shown by the use of a 15 year time horizon which increased the with-PAS ICER to £47,294.

- The ICER was sensitive to the way in which treatment effects were measured. Using the reciprocal of serum creatinine (as used in the base case) rather than CKD-EPI eGFR resulted in a lower ICER; however, CKD-EPI eGFR results are more likely to be used in clinical practice and are thus the relevant findings on which to base the analysis; with this method, the with-PAS ICER rose to £29,356.
- The base case result did not allow for an on-treatment disutility, which may be optimistic given the side effect profile associated with treatment. Applying a disutility (0.0025) increased the with-PAS ICER to £12,915.
- The base case used a disutility value for dialysis that did not accord with the source paper. Correcting for this increased the with-PAS ICER to £12,658.
- The company provided a sensitivity analysis which combined the three sources of uncertainty above (i.e. using the CKD-EPI measure, applying an on-treatment disutility and correcting for the dialysis disutility). This resulted in a with-PAS ICER of £30,677. There was also some potential uncertainty from double-counting of costs for the post-transplant states through the application of both disease management costs and costs of treatments within these states. While not all background costs would be captured in treatment costs, the analysis does show sensitivity to this parameter; at 50% of the assumed base case value, the ICER in the combined sensitivity analysis was £32,920.
- Utility values from a ADPKD-specific study have recently become available. Using these values increased the with-PAS ICER for the combined sensitivity analysis above slightly to £33,531. Applying the 95%, 90% and 85% adjustments to account for potential uncertainty in long term treatment effects to this combined analysis gave with-PAS ICERs of £34,584, £41,463 and £44,436 respectively.
- The company provided exploratory subgroup analysis according to the CKD stages 1 to 3. While caution should be exercised in considering the results which are based on small patient numbers, the results (using the company's base case assumptions) showed that the with-PAS ICERs ranged from £137,770 in CKD1 patients to dominant in CKD3 patients.
- The analysis does not account for the potential for cases of serious hepatic side effects. However, the company did provide some additional analysis on their base case to account for this and the impact on the ICER was very small as the number of cases was low.

The Committee considered the benefits of tolvaptan in the context of its decision modifiers that can be applied when encountering high cost-effectiveness ratios and where there is increased uncertainty due to the orphan-equivalent status of the medicine and concluded that the criterion for absence of other treatment options of proven benefit was met.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate modifiers, the Committee was able to accept tolvaptan for use in NHS Scotland.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- Submissions were received from Kidney Research UK and the Polycystic Kidney Disease Charity, which are both registered charities.

- Both Kidney Research UK and the Polycystic Kidney Disease Charity have received pharmaceutical company funding in the past two years, with both having received funding from the submitting company.

- ADPKD is a life-threatening genetic disease with multiple clinical effects and has significant lifestyle, emotional and socio-economic implications for patients, their extended families, friends and the NHS. Patients suffer from symptoms such as fatigue, enlarged abdomen, severe pain (especially as the kidneys develop a larger cyst burden) and infections. Other organs may also be impacted and kidney failure is a reality in many patients. ADPKD is dominantly inherited, meaning that its impact is experienced across generations and many patients feel guilt about passing on the disease to their children.

- Currently ADPKD management is restricted to symptomatic control, including anti-hypertensive medication, antibiotics to deal with urinary and cyst infections, and analgesics to help alleviate pain. Tolvaptan is the first medicine to address the underlying cause.

- To date, management of the ADPKD has been entirely symptomatic and tolvaptan is the first therapy to offer the potential for slowing disease progression, giving new hope to affected patients, their families and their future generations.

Additional information: guidelines and protocols

There is no current guidance on the treatment of ADPKD. The Kidney Disease: Improving Global Outcomes (KDIGO) group published an executive summary report in 2015: Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. It does not include any recommendations on the management of ADPKD, but has identified areas of consensus, knowledge gaps and research and health-care priorities.[5]

Additional information: comparators

There are no relevant comparators.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Tolvaptan	Initially 45mg orally before breakfast and 15mg eight hours later. To be titrated if tolerated, with at least weekly intervals between titrations to 60mg+30mg daily and then to a target regimen 90mg+30mg daily.	15,707

Cost from eMIMS on 26 August 2015. Cost does not take any patient access scheme into consideration.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 284 patients in year 1 and 289 in year 5**.** Based on an estimated uptake of 1% in year 1 (3 patients) and 50% in year 5 (136 patients), the impact on the medicines budget was estimated at £43k in year 1 and £2.1m in year 5 without the PAS. There were no displaced medicines costs but as treatment with tolvaptan is associated with additional tests and monitoring, when these costs were included, the net budget impact was £45k in year 1 and £2.2m in year 5.

SMC expert responses suggest that the patient uptake figures may be an underestimate.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1. The European Medicines Agency (EMA) European Assessment Report, tolvaptan. (Jinarc®). 26 February 2015, EMEA/H/C/002788/0000
2. Torres VE, Chapman AB, Devuyst O et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease plus Supplementary Appendix. New England Journal of Medicine. 2012; 367 (25):2407-18
3. Tolvaptan tablets (Jinarc®) Summary of product characteristics. Otsuka Pharmaceuticals (UK) Ltd. Electronic Medicines Compendium Last updated 10 June 2015
4. Wuthrich RP, Serra AL, Kistler AD. Autosomal dominant polycystic kidney disease: new treatment options and how to test their efficacy. Kidney & blood pressure research. 2009;32 (5):380-7.
5. Chapman AB, Devuyst O, Eckardt K-U et al. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference plus Supplemental Appendix Kidney International 2015, 88, 17–27

This assessment is based on data submitted by the applicant company up to and including 16 October, 2015.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.